Copper Mediated Reversible Deactivation Radical Polymerization in Aqueous Media

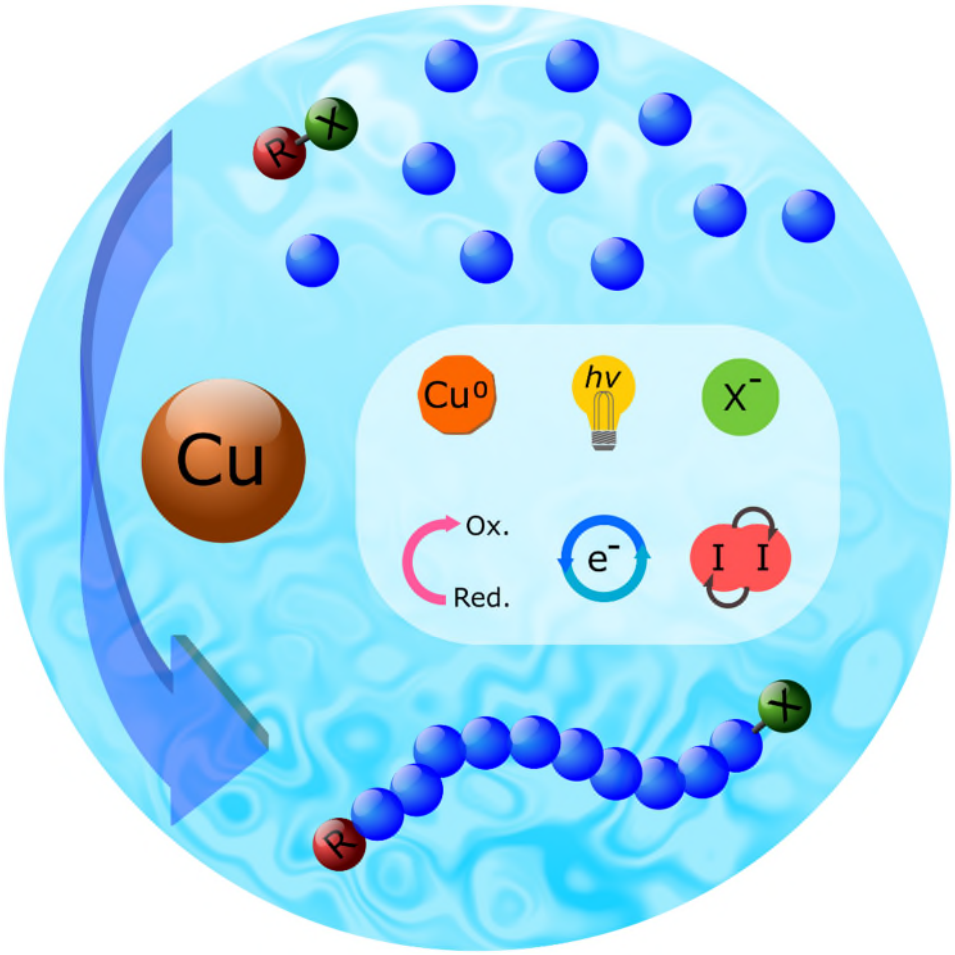
Glen R. Jones*[a], Dr Athina Anastasaki[b], Richard Whitfield[a], Nikolaos Engelis[a], Evelina Liarou[a], Professor David M. Haddleton*[a]

[a]University of Warwick, Department of Chemistry, Library Road, Coventry, CV4 7AL

[b]Materials Research Laboratory, University of California, Santa Barbara, California, 93106, USA

*glenrichardjones@gmail.com, *d.m.haddleton@warwick.ac.uk

Key advances within the past 10 years have transformed copper mediated radical polymerization from a technique which was not very tolerant to protic media into a range of closely related processes capable of control over the polymerization of a wide range of monomers in pure water at ppm catalyst loadings; yielding water soluble macromolecules of desired molecular weight, architecture and chemical functionality, with applications ranging from drug delivery to oil field recovery. In this review we highlight and critically evaluate the synthetic methods that have been developed to control radical polymerization in water using copper complexes, identify future areas of interest and challenges still to be overcome.



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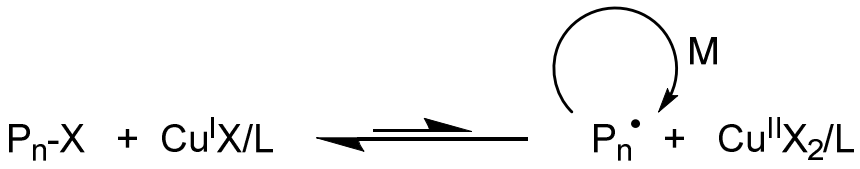
1. Introduction

Attaining a high degree of control over molecular weight, macromolecular architecture and chemical functionality using radical polymerizations has been a long standing goal in polymer chemistry. This was realized to certain extents in the 1990's with the advent of reversible

deactivation radical polymerization (RDRP) techniques. Broadly speaking, the chemistry of an RDRP is *via* a free radical propagating species which exists in an equilibrium with dormant species. Whilst only a small proportion of chains are actively propagating at any one instant in time, the interconversion between active and dormant states is relatively fast. This results in the same probability of growth for each chain yielding polymers with narrow molecular weight distributions (dispersity) and a number average molecular weight directly correlated with the ratio between monomer and initiator/RDRP agent.

A particular advantage of RDRP is the ability to control polymerization of vinyl monomers in aqueous media. The need for sustainable, high capacity and arguably environmentally friendly chemical processes has led to an increase in the use of water as a reaction medium.[1] If a solvent is to be used for a chemical reaction, water is inexpensive, non-toxic and readily available. Water also has many unique properties which suit it to a wide range of chemistries and substrates: its high specific heat capacity is ideal for reactions which are exothermic, the solubility of salts allows for many additional effects such as salting-in or salting-out, pH can be simply varied, solutions can be buffered, and co-solvents can be utilized to further increase solubility and monomer scope. Crucially, the use of water as a reaction solvent is the ideal medium for biologically oriented applications – water is the preferred solvent for natural processes.



Scheme 1. Simplified mechanism of atom transfer radical polymerization (ATRP).

Three main techniques have emerged as the most viable for the polymerization of hydrophilic monomers in aqueous media: nitroxide mediated polymerization (NMP),[2] reversible addition fragmentation chain transfer (RAFT) polymerization,[3] and copper mediated polymerization approaches (ATRP, scheme 1).[4] Both RAFT and NMP have been successfully reported to proceed in aqueous media with relatively few restrictions, yielding well-defined polymers with narrow molecular weight distributions and high end group fidelity. On the contrary, copper mediated polymerization approaches have appeared to be much more sensitive under aqueous conditions and for a long time were considered too challenging to achieve. However, owing to the additional benefits offered through these strategies, including the possibility to run the

polymerizations at very low temperatures and the facile functionalization of the halide end group, significant attention has been drawn.

Numerous reviews cover ATRP in heterogeneous aqueous media (i.e. dispersed systems),[5] but to the best of our knowledge none focus on the advances that have been made in copper mediated RDRP in aqueous *solution*. This review will focus on the developments of copper mediated RDRP in homogeneous aqueous media with emphasis given on how to produce well-defined polymeric materials. Challenges and associated solutions encountered upon conducting copper mediated polymerization in aqueous media will be critically discussed and evaluated. The mechanism of this chemistry in aqueous media as well as Iron and Ruthenium Mediated polymerization has been reviewed elsewhere and will not be the subject of this review.

2. General Considerations for Copper Mediated Polymerization in Aqueous Media

2.1. Desirable Qualities in Aqueous Polymerization Systems

A number of desirable qualities describe an ideal polymerization system in aqueous media. Broadly speaking: low copper catalyst concentration, high monomer conversions (ideally >90%), high end group fidelity and low temperatures have all been targets of recent developments in the field.

Low catalyst concentration is of importance for two main reasons; to reduce cost and to avoid metal contamination of the final material. Using less catalyst enables a more commercially exploitable technique, with recent work reducing catalyst concentrations to parts per million (ppm) levels in aqueous media.[6] Copper can discolour polymers green/brown (depending on the ligands present) thus additional purification techniques to remove metal contamination from polymeric products are required. High purity is also particularly required for electronic and biologically orientated applications and a reduction in catalyst concentration can aid in the facile preparation of these materials.[7] It is noted copper(II) salts are classified as GRAS (Generally Regarded As Safe) by the FDA and listed as an essential trace element for most plant and animal species.[8] However, despite the disadvantage of residual catalyst (including metal and coordinating ligands), the most toxic component of a radical polymerization is the monomer (usually activated vinyl monomers such as (meth)acrylates or (meth)acrylamides). For this reason high monomer conversion is highly desirable as it allows for fewer or less stringent purification procedures to be used which saves time, energy and reduces cost. Another benefit of being able to achieve near quantitative conversions with Cu-mediated polymerization

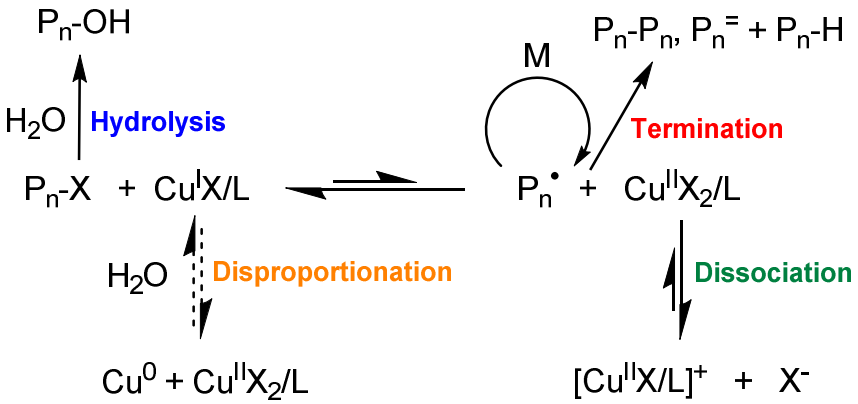
is the possibility of *in-situ* chain extensions to form complex macromolecular architectures. If polymerization proceeds to high conversion with high end group fidelity (minimal loss of the ω-end group functionality), the synthesis of well-defined block copolymers in a one pot process can be achieved by iterative sequential monomer addition, eliminating the need for intermediate purification steps and thus significantly speeding up the process.

Low temperature polymerization methods are of importance as they allow for the synthesis of polymers that exhibit thermoresponsive behaviour above certain temperatures in aqueous media (*e.g.* PNiPAm) as well as allowing for polymerization to occur in the presence of biological molecules which could potentially be denatured at elevated temperatures (*e.g.* enzymes and therapeutically relevant polypeptides.) Lower temperatures are also favourable in a number of cases to suppress side reactions.[9] The tertiary alkyl halide initiators/propagating chains in most Cu-mediated RDRP's can also undergo side reactions such as hydrolysis or elimination in aqueous media, resulting in loss of functionality, which is exacerbated at higher temperatures. Chain-end hydrolysis is discussed in further detail in section 2.2.

Another more recent consideration in RDRP has been the potential to introduce external stimuli to control the polymerization. Specifically, light, mechanical, and electrochemical stimuli have been demonstrated to achieve impressive temporal control by switching the polymerization "on" and "off" upon demand whilst maintaining narrow molecular weight distributions and high end group functionality, as discussed in subsequent sections of this review.[10]

2.2. Challenges in Conducting Copper Mediated Polymerization in Aqueous Media

ATRP has been reported to have many limitations when carried out in aqueous media. Reactions were generally found to be faster and exhibit a lower degree of control over chain length and molecular weight distributions which was ascribed to higher radical concentration leading to higher rates of radical-radical reaction and side reactions. A number of complex processes and equilibria which fundamentally control the catalytic process, thereby altering K_{ATRP} in water are shown in scheme 2: hydrolysis or elimination of the R-X or P-X bond, disproportionation of Cu(I) species to Cu(0) and Cu(II), dissociation of the deactivating Cu(II) species, and conventional radical-radical termination reactions.



Scheme 2. Mechanism of ATRP with potential side reactions and equilibria in aqueous media: *blue*: hydrolysis of alkyl halide chain end, *red*: radical-radical termination reactions, *orange*: disproportionation of Cu(I), *green*: dissociation of halide from Cu(II) complex.

Perhaps the most significant side reaction associated with ATRP and copper mediated RDRP in aqueous media is the solvolytic displacement of halide ligands from deactivating Cu(II) complexes. For a controlled radical polymerization to take place the concentration of radicals must remain low in order to reduce radical-radical termination reactions, obviously second order in [radical]. With ATRP the [radicals] is dictated by K_{ATRP} which can be expressed as k_{act} / k_{deact}. k_{deact} (governed by the concentration of halide containing 'deactivating' Cu(II) species) must be higher than k_{act} in order to keep radical concentration low. In aqueous media a problem arises because the highly polar nature of water aids the solvation of halide ions through the formation of hydrogen bonds. This can result in a very high proportion of Cu(II) species, depending on the ligands used, which cannot transfer a halide to a propagating polymer chain. Electrochemical investigation of activation and deactivation rates in aqueous media for common catalyst systems by Fantin *et al.* demonstrate that deactivation by dissociated complex is in fact highly efficient, but is hampered by the weak Cu-X bond.[11] It has been suggested that the free coordination site is then occupied by solvent[12] or by polar monomers.[11, 13]

Hydrolysis of the alkyl halide at the ω chain end can be a significant problem in aqueous media which results in a loss of end group fidelity as the hydroxyl terminated polymer is unable to participate in further chain growth. This results in dead chains and broadening of the molecular weight distribution. The rate of hydrolysis in Cu-RDRP's has been demonstrated to be effectively independent of copper concentration,[14] indicating that copper mediated hydrolysis is not significant, but is of course dependent on the halide (R-Br is more readily hydrolyzed than R-Cl) and the nature of the monomer used (*i.e.* the nature of the alkyl halide polymer chain end). Hydrolysis can be particularly problematic in the polymerization of acrylamides, in which

it has been postulated that the nitrogen atom present in the penultimate monomer unit undergoes an intramolecular substitution reaction with the polymer chain end, giving a cyclized structure highly susceptible to hydrolysis.[15] Rapid disproportionation of Cu(I) to Cu(II) and Cu(0) in water is a further factor that complicates aqueous Cu-RDRP. Although disproportionation in many organic solvents *e.g.* toluene and acetonitrile is not appreciable, in highly polar aqueous media and in the presence of many common ligands it can be significant. Initially, disproportionation was presented as an undesirable side reaction which should be avoided, however, recent work showed that it can in fact be beneficial under certain conditions (see section 5.)

All of these processes can contribute to unbalancing the RDRP equilibrium, resulting in 'dead' chains from hydrolysis, altered activator and deactivator concentrations from disproportionation, and loss of deactivating species from dissociation. The net effect of this is often seen as a fast polymerization rate and poor control over molecular weight and molecular weight distributions. Over the past 20 years different approaches to copper mediated RDRP have been developed which overcome these issues, as described in sections 3, 4, and 5 of this review.

3. Conventional ATRP in Aqueous Media

Conventional (or normal) ATRP is defined here as a process where Cu(I) is directly introduced (and NOT generated *in situ*) in the reaction mixture before the beginning of the polymerization. On many occasions, an additional amount of Cu(II) is also added in the reaction mixture. Early work concerning conventional ATRP indicated that the process was not very tolerant to protic media. A series of reviews discussing controlled/'living' polymerization from 2001 cite very few successfully controlled ATRP processes in water.[5] One of the first reported examples is the polymerization of hydroxyethyl acrylate (HEA) in the presence of 2,2-bipyridine (bpy), by Matyjaszewski and coworkers in 1998.[16] Initial, experiments were carried out in bulk furnishing conversions of ~90% with dispersity values as low as 1.15 measured by size exclusion chromatography (SEC). When the same experiments were repeated in aqueous solution (HEA:H_2O, 1:1 v/v), broader molecular weight distributions ($Đ$ > 1.30) were obtained.[16]

In 1999, utilizing a similar system of bpy with Cu(I)Cl and Cu(I)Br, Armes and coworkers reported the rapid polymerization of poly(ethylene glycol) methyl ether methacrylate (PEGMA) in aqueous solution.[17] Reactions were conducted at 20 °C (the first examples of

room temperature aqueous ATRP) and high conversions (>95%) were obtained in short time periods (~20 minutes) with dispersities as low as 1.12.[18] Selected reactions carried out in bulk were found to be significantly slower than analogous reactions in aqueous media. It was postulated that differences in the formed copper complexes in water are the reason for the observed rate acceleration. Similar conditions were also reported to control the polymerization of sodium methacrylate (NaMA) and 2-(dimethylamino)ethyl methacrylate (DMAEMA), albeit with significantly lower conversion and higher dispersities, attributed to loss of catalyst activity through reactions with the functional monomer.[19]

Pyridyl methanimines, as developed by the Haddleton group, showed a number of advantages over bpy in organic media such as being particularly effective for the polymerization of low k_p monomers such as methacrylates.[20] In a collaboration between Armes and Haddleton, ligands of this type were used that formed soluble complexes with copper in aqueous solution.[21] PEGMA was polymerized at 20 °C to high conversions (>90%) in a period of just 5 minutes, with dispersities between 1.10-1.40. Although pyridyl methanimines might not be expected to be stable to hydrolysis, the high rate of polymerization means that hydrolysis is negligible within the timeframe of the reaction and no ligand hydrolysis was observed. This is further supported by reactions carried out at higher temperatures, which exhibited faster rates but broader molecular weight distributions.[21]

Poly(acrylamides) have proved to be much more difficult to synthesize by conventional ATRP in aqueous media.[15, 22] In 2003 Jewrajka and Mandal reported the ATRP of acrylamide (AAm) in aqueous and mixed aqueous/glycerol systems.[23] Both alkyl chloride and bromide initiators with bpy both resulted in poor control over polymerization, with dispersities around 1.7 and low molecular weight tailing evident in SEC chromatograms. A later report using PMDETA as the ligand achieved a higher degree of control over polymerization ($Đ$ as low as 1.24), albeit at severely limited conversions (9% in 48 h).[24] Similar trends were also noted by Jiang *et al.* using a tetramethylethylenediamine (TMEDA) ligand, with conversions below 20% in most cases and dispersities between 1.2-1.6.[25] More recently, Broekhuis and coworkers reported the polymerization of AAm and NiPAm using a Cu(I)X/tris[2-(dimethylamino)ethyl]amine (Me_6Tren) catalyst (figure 1).[26] The process exhibited a linear increase of molecular weight with conversion and reactions proceeded to relatively high conversions, however the degree of control ($Đ$ > 1.4) is significantly poorer than that normally exhibited for ATRP of (meth)acrylates in organic media.

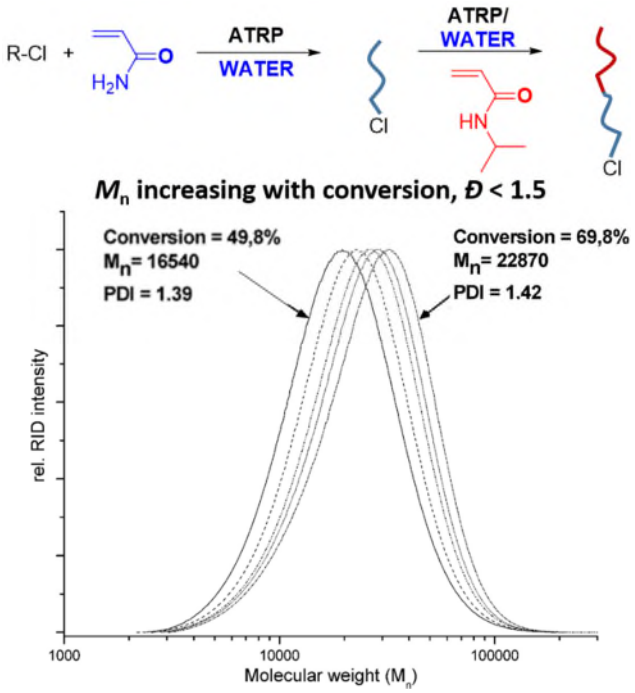
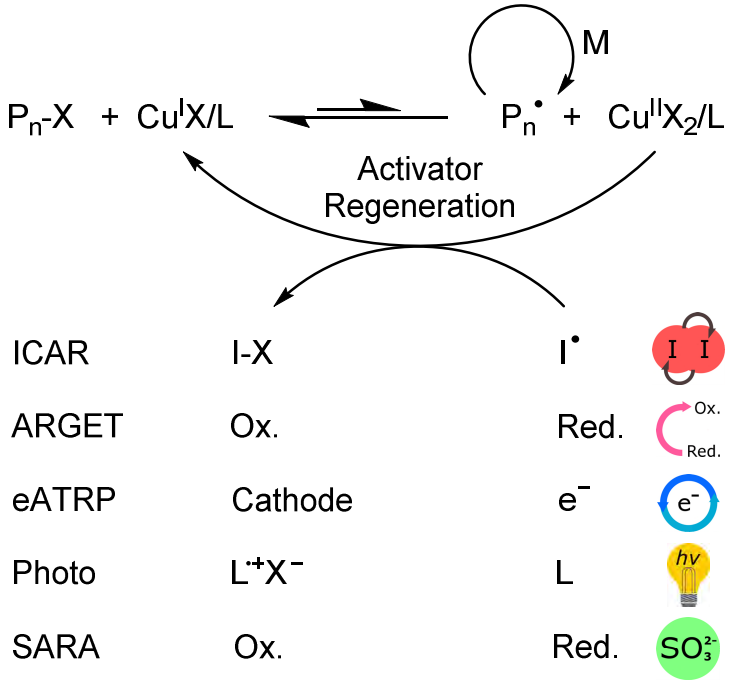


Figure 1. ATRP of AAm and NiPAm in aqueous media. Figure adapted with permission from reference 26. Copyright 2012 American Chemical Society.

Despite some success, particularly with water soluble methacrylates, conventional ATRP in aqueous environments has been shown to have significant drawbacks such as limited monomer scope (acrylamide polymerization is not reported to be controlled) and limited demonstration of end group fidelity. Additionally, despite control over the chain length and dispersity of the products in certain cases, all of the examples of normal ATRP in aqueous media described above use at least stoichiometric amounts of copper(I) halide and ligand with respect to the number of polymer chains. As described in section 2.1, high copper concentrations (typically ~5000 ppm or higher) can be disadvantageous due to the added cost of purification, potential toxicity, and discolouration of products. Higher catalyst concentrations are necessary in conventional ATRP due to the high concentration of radicals present during the establishment of the ATRP equilibrium which leads to radical-radical termination events resulting in an associated increase in deactivator and decrease in activator, known as the persistent radical effect (PRE).[27] Using stoichiometric amounts of catalyst ensures there is still sufficient activating species present at equilibrium. A further reason, particularly noteworthy for polymerization in aqueous media, is that higher concentration of Cu(II) species in solution will lessen the observed effect of dissociation, whereby the concentration of halide containing deactivating Cu(II) species at the dissociation equilibrium is still sufficient to control polymerization; as discussed in section 2.2. A number of different approaches have been

subsequently developed which utilize external stimuli, either chemical or physical, to regenerate the active species lost during the initial stages of ATRP (scheme 3), hence allowing for much lower catalyst concentrations to be employed (section 4).

4. Activator Regeneration Methods in Aqueous Media



Scheme 3. Scheme depicting the numerous methods of activator regeneration used in ATRP.

4.1 Initiators for Continuous Activator Regeneration (ICAR) ATRP

Initiators for continuous Activator Regeneration (ICAR) ATRP, first reported in the mid 2000's, uses a small amount of free radical initiator which can abstract the bromine atom from Cu(II) deactivating species to generate Cu(I) activating species. The continuous regeneration of activating species from deactivating species[28] facilitated by the radical initiator allows for much lower copper concentrations to be used compared to normal ATRP.[29] In 2012, Konkolewicz *et al.* successfully reported the first example of ICAR ATRP in water (figure 2).[6c] In the presence of low copper concentrations (<100 ppm well-defined poly(PEGMA) was obtained with dispersities between 1.09 and 1.56 (M_n = 37-70 kDa.) The key to controlling polymerization was found to be addition of a bromide salt, tetraethylammonium bromide ($Et_4N^+Br^-$), which reduced the dispersity of the products from ~2 to as low as 1.09. This is attributed to the bromide ion promoting the formation of the Cu(II) deactivating complex, as supported by an associated decrease in rate with increasing salt concentration. The work also demonstrated the synthesis of a thermoresponsive block copolymer. Poly(PEGMA) (M_n = 16.5

kDa, $Đ$ = 1.41) was synthesized and then isolated to yield a macroinitiator used in the further ICAR ATRP of poly(ethylene oxide) methyl ether acrylate (PEGA) resulting in a block copolymer (M_n = 40 kDa, $Đ$ = 1.39). Although block copolymer synthesis was successful the dispersity of the obtained block was 1.39, which is relatively broader than other examples in aqueous media by other Cu-RDRP techniques, this is likely to be due to the homopolymerization of PEGA initiated by the ICAR agent, as discussed in the original report of ICAR ATRP.[29] Thus, ICAR ATRP is a promising technique for controlled polymerization in aqueous media, but drawbacks including the sacrifice of end group fidelity and dispersity due to the addition of the free radical initiator would seem to limit its applicability for the synthesis of high order macromolecular architectures.

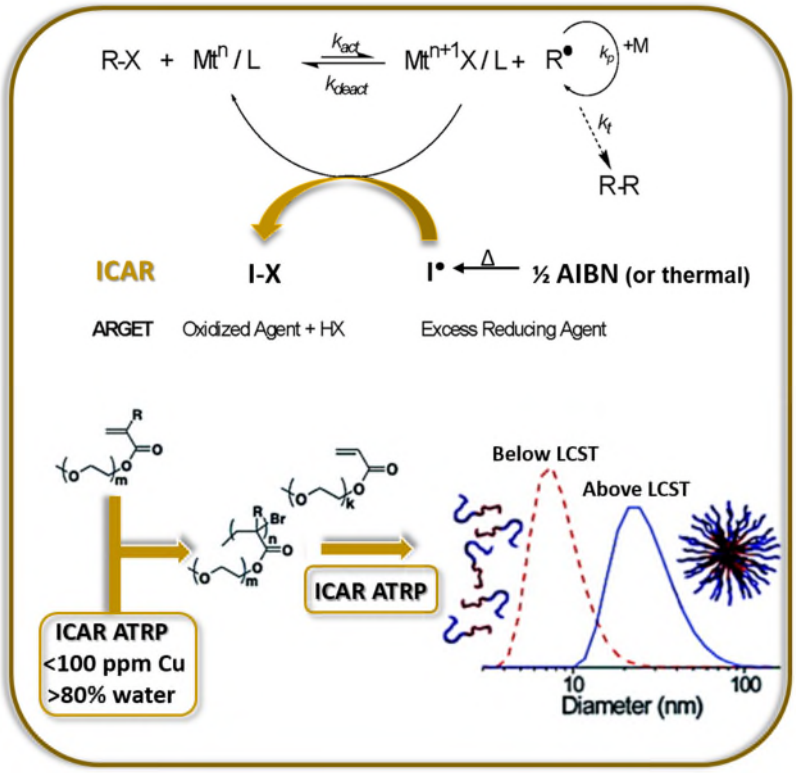


Figure 2. Representation of ICAR ATRP in water to synthesize thermoresponsive block copolymers. Figure adapted with permission from reference 6c. Copyright 2012 American Chemical Society.

4.2. Activators (Re)Generated by Electron Transfer (AGET/ARGET) ATRP

Activators generated by electron transfer (AGET) ATRP is a process whereby activator (Cu(I) species) is generated from an oxidatively stable Cu(II) species through utilization of a reducing agent. The process was first reported to effectively control polymerization in water in 2006 by Matyjaszewski and coworkers.[30] Using the air stable Cu(II)/TPMA, ascorbic acid was used as a reductant to facilitate the *in-situ* generation of a Cu(I) complex yielding poly(PEGMA) with

molecular weights of up to 87 kDa with dispersities lower than 1.3. In 2011 Averick *et al.* reported polymerization of PEGMA from bovine serum albumin (BSA) modified to contain alkyl halide initiating motifs in biologically relevant aqueous media, later expanded upon by Maynard and coworkers.[31] Polymerization was carried out at 30 °C in phosphate buffer solution (PBS), with Cu(II)/TPMA and ascorbic acid (figure 3). SEC analysis of polymers after cleavage from the protein yielded dispersities of 1.19, with an M_n of 83 kDa. Synthesis of protein-polymer hybrids (PPH's) by this 'grafting-from' approach is one of the key benefits of aqueous ATRP techniques, however copper concentrations in the reaction were very high, with 10 equivalents of Cu(II) per equivalent of initiator, meaning extensive purification of the final PPH was required.

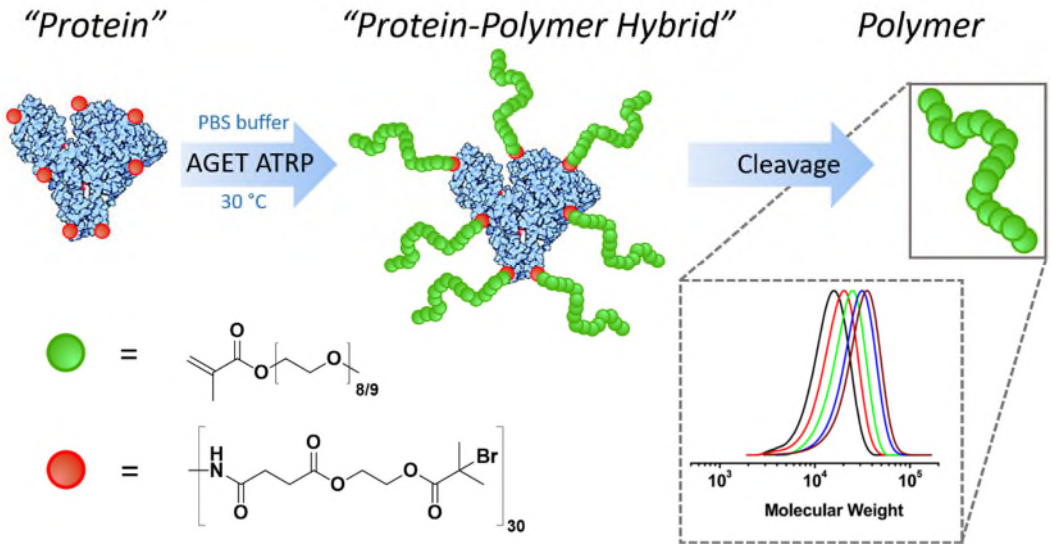


Figure 3: Synthesis of PPHs via (AGET) ATRP from [BSA]-O-iBBr$_{30}$ and Selective Cleavage of Polymer. Figure adapted with permission from reference 31a. Copyright 2012 American Chemical Society.

Activators regenerated by electron transfer (ARGET) ATRP follows a similar concept to AGET. In ARGET the reducing agent is slowly fed into the reaction, thus allowing for lower copper concentrations to be utilized, as (re)generation of Cu(I) from Cu(II) can occur throughout the reaction. Commonly employed reducing agents include FDA approved tin(II) 2-ethylhexanoate (Sn(EH)$_2$), ascorbic acid, and reducing sugars such as glucose.[32] In contrast to ICAR, ARGET is better suited to the preparation of block copolymers as the means of reducing deactivator cannot initiate homopolymerization during the formation of the second block.

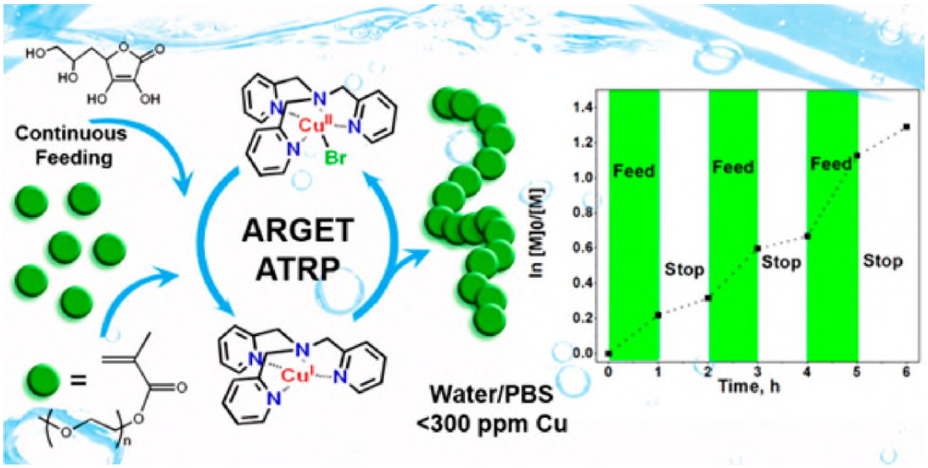


Figure 4: Aqueous ARGET ATRP of PEGMA utilizing Cu/TPMA catalyst system, demonstrating temporal control. Figure adapted with permission from reference 33. Copyright 2012 American Chemical Society.

Aqueous ARGET ATRP was first reported in 2012 by Matyjaszewski and coworkers.[33] As opposed to ARGET ATRP carried out in organic media, aqueous ARGET ATRP is much more sensitive and relies on a number of factors including gradual feeding of the reducing agent and addition of a simple halide salt. A Cu/TPMA catalyst system was selected due to its stability at low concentrations and negligible disproportionation in aqueous media. It was demonstrated that feeding of the reducing agent (ascorbic acid) so that reduction occurred at a steady rate throughout the polymerization gave better control, in line with previous studies.[31a] Experiments in which feeding was not used resulted in poor control, attributed to significant termination events with the Cu/TPMA catalyst. In agreement with the previously discussed report on aqueous ICAR ATRP it was found that ARGET ATRP also required the presence of a halide salt in solution to provide halide ions which promote deactivator formation. Polymerization of PEGMA proceeded to conversions of ~70% with dispersities of 1.3 and below at a reaction temperature of 30 °C. Temporal control of the reaction was demonstrated by stopping and starting the feed of reducing agent, with a decrease in rate associated with the ceased addition of ascorbic acid (figure 4), although the control was not as pronounced as other techniques which have since been developed.

4.3 Electrochemically Mediated (eATRP)

Electrochemical ATRP (*e*ATRP) reversibly generates Cu(I) species from air-stable Cu(II) by applying an electrochemical potential.[34] Varying the applied potential can effectively control the rate of polymerization. Furthermore, cycling between time periods of applied potential and periods of no potential show that polymerization is slowed when electrochemical regulation was not employed, demonstrating a degree of temporal control over the reaction.

Following on from the initial report of copper based *e*ATRP in organic media, Matyjaszewski and coworkers expanded the technique to the polymerization of PEGMA in aqueous media.[35] Reactions were conducted with a Cu/TPMA catalyst in water with various electrolytes including tetraethylammonium tetrafluoroborate ($Et_4N^+BF_4^-$), PBS buffer and $Et_4N^+Br^-$. As with the polymerization of methyl acrylate (MA) reported in organic media, increasing the magnitude of the applied potential was found to increase the rate of the polymerization, however in aqueous media it was found that a high rate had negative consequences on the degree of control over the polymerization. E_{App} of -0.55 V (*vs.* standard calomel electrode) yielded poly(PEGMA) with a dispersity of 1.58, decreasing E_{App} to -0.31 V decreased the rate of polymerization but had little effect on the degree of control ($Đ$ = 1.53). Further reduction of E_{App} to -0.21 V again showed a decrease in rate but with a marked increase in control ($Đ$ = 1.16) at 99% monomer conversion. Low levels of control at higher applied potential is attributed to increased bimolecular termination reactions at higher radical concentrations. One of the drawbacks of this protocol is the use of platinum electrodes, which is present an obstacle to larger scale synthesis due to cost. In 2016 Isse and coworkers demonstrated that *e*ATRP could also be conducted with non-noble metals such as NiCr and stainless steel by using a simplified reaction setup (an undivided cell and galvanostatic mode).[36]

Aqueous *e*ATRP has also been reported to control the polymerization of acrylamides, significant due to the inability of many other ATRP techniques to effectively control the polymerization of this class of monomer.[37] In one report Chmielarz *et al.* investigated polymerization of AAm in mixed aqueous media (10 % v/v dimethyl formamide (DMF)). Of the catalysts employed, Cu/Me_6Tren catalyst system exhibited the best degree of control ($Đ$ as low as 1.09). *In-situ* chain extension with NiPAm demonstrated retention of the halide end group, however conversions of AAm were not reported to be quantitative, resulting in the second block being a statistical copolymer of AAm and NiPAm. Chain extension by means of isolating a polyacrylamide macroinitiator was not reported, indicating that aqueous *e*ATRP is perhaps not an ideal approach for the synthesis of well-defined acrylamide block copolymer architectures.

4.4 Photoinduced ATRP

External regulation of RDRP's by photochemical mediation has attracted considerable attention in recent years due to wide availability, environmental benignity and the possibility of simple switching between active and dormant states.[10, 38] Copper mediated photo-ATRP

relies on free amine ligand in solution that is able to reduce Cu(II) species to Cu(I) when in a photoexcited state.

Photoinduced ATRP was first reported in aqueous media in 2015 by Matyjaszewski and coworkers, promoted by visible light and a Cu(II)X_2/TPMA catalyst.[6a] PEGMA was able to be polymerized to high molecular weights (M_n > 100 kDa) with dispersities as low as 1.07. The key to controlling the reaction was found to be addition of an additional halide salt, which offsets the dissociation of Cu(II) species in aqueous media, as discussed in section 2.2. End group fidelity was demonstrated through chain extension of an isolated macroinitiator with a lower molecular weight PEGMA monomer to yield block copolymers with high molecular weight (M_n = 139 kDa, $Đ$ = 1.22). Temporal control was also demonstrated by cycling the reaction between periods of illumination and darkness.

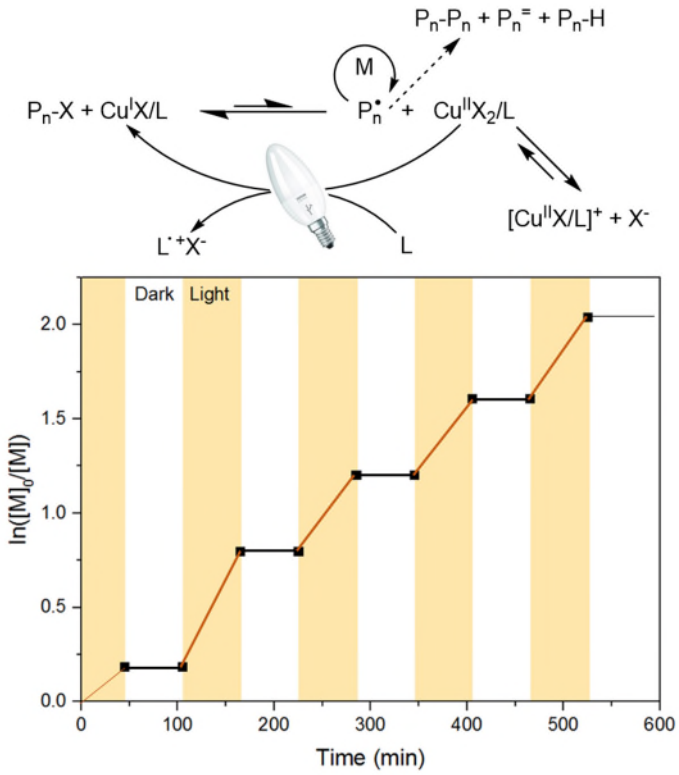


Figure 5: Scheme demonstrating reduction of Cu(II) by photoexcitation of ligand in photo ATRP, and demonstration of temporal control. Figure adapted with permission from references 6a and 6b. Copyright 2015 & 2016 American Chemical Society.

An initial report by Haddleton and coworkers of photo polymerization of acrylates using a UV activated Cu(II)Br_2/Me_6Tren catalyst system found that reactions using these conditions were uncontrolled in water with dispersities >2, despite the high degree of control and synthetic versatility seen in organic media.[39] A later investigation into aqueous photopolymerization

utilizing this catalyst system found that drastically increasing the catalyst concentration was able to effectively control the polymerization of PEGA, indicating that dissociation of the Cu(II)X_2/L species is responsible for the poor control initially observed.[6b] Catalyst concentrations were reduced significantly whilst maintaining control over the polymerization by addition of sodium bromide, whereby the addition of excess free halide in solution drives the dissociation equilibrium to the dissociated species capable of deactivating propagating radicals (see section 2.2.) Three equivalents of sodium bromide with respect to initiator resulted in poly(PEGA) with dispersities as low as 1.11 at a copper concentration of 67 ppm. Control over polymerization was demonstrated at copper concentrations as low as 26 ppm. The technique was also demonstrated to be able to polymerize HEA and 3-sulfopropyl acrylate potassium salt with a similar degree of control. Quantitative monomer conversion was achieved for all polymerizations of PEGA, a feature which was exploited for an *in-situ* chain extension to demonstrate high end group fidelity. Temporal control over the reaction was found to be good, with no conversion of monomer detected during periods in which the reaction vessel was transferred to a dark room (figure 5), even over an extended period of time (6 hours).

4.5 Supplemental Activator and Reducing Agent (SARA) ATRP

Supplemental activator and reducing agent (SARA) ATRP utilizes a species which can reduce deactivator to activator in a similar manner to ARGET (section 4.2), whilst also activating alkyl halides independent of other ATRP components. Most reports concerning SARA ATRP utilize Cu(0) as the SARA agent, however due to the large body of work associated with aqueous RDRP in the presence of Cu(0) and the mechanistic debate within the literature,[4b] Cu(0)-RDRP is treated separately in section 5.

Matyjaszewski and coworkers introduced inorganic sodium sulfites (a common additive in wine making) as SARA agents, which have been demonstrated to reduce Cu(II) to Cu(I) and activate alkyl halides.[40] Polymerization of MA in organic media was demonstrated using various sulfites with a $CuBr_2$/Me_6Tren catalyst. More recently sodium sulfites have been utilized for SARA ATRP in aqueous media, as shown in figure 6.[41] Aqueous SARA ATRP was carried out using TMPA instead of Me_6Tren, in an effort to avoid disproportionation of Cu(I) formed from reduction of Cu(II). Both PEGA and PEGMA were polymerized with dispersities of ~1.20 and the polymerization rate could be slowed by stopping the feeding of sulfite.

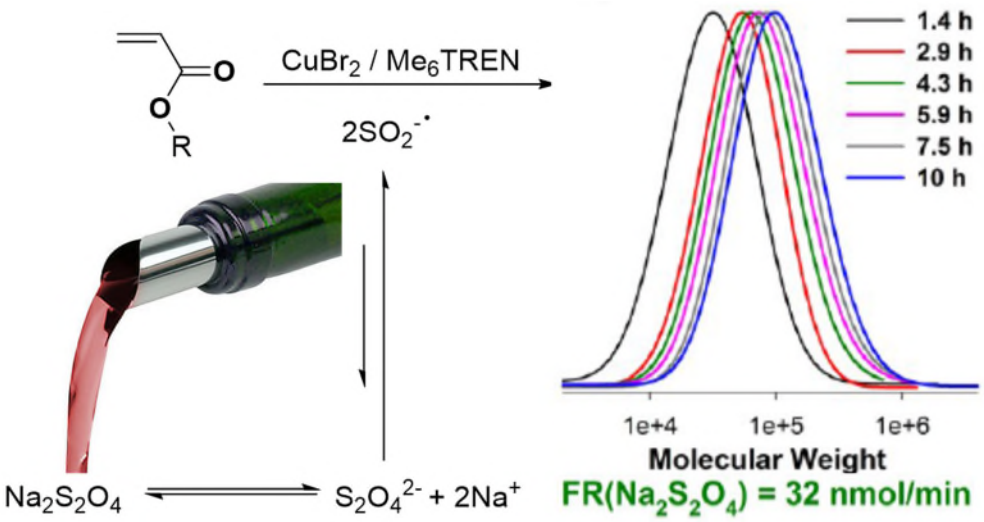


Figure 6: SARA ATRP utilizing sodium sulfite, a common additive in wine making, to reduce Cu(II) and form radicals from alkyl halides. Figure adapted with permission from reference 41. Copyright 2017 Royal Society of Chemistry.

5. Aqueous RDRP in the Presence of Metallic Copper (Cu(0)-RDRP)

RDRP in the presence of metallic copper was first reported Matyjaszewski in 1997 for bulk polymerizations,[42] with the intention of utilizing Cu(0) as a reducing agent to reform Cu(I) from Cu(II) during polymerization in a process similar to ARGET-ATRP. Matyjaszewski and coworkers noted enhanced rates and control over polymerizations in which Cu(0) was present. In 2006 Percec and coworkers reported an "ultrafast" polymerization system using Cu(0) in dimethyl sulfoxide (DMSO).[43] Cu(0) mediated techniques in water can be broadly differentiated by the source of Cu(0) in the reaction, either externally added sources such as copper wire or powder, or *in-situ* generated particles through disproportionation or reduction reactions of higher oxidation state copper species.

5.1 Externally added Cu(0)(wire and powder)

The first reported method of conducting Cu(0)-RDRP in water was through use of an external source of Cu(0), commonly in the form of copper wire or copper powder. Early examples include the polymerization of DMAm and NiPAm in a mixed solvent system of methanol (MeOH) and water.[44] Experiments with increasing water concentration dramatically increased the dispersity of the final product ($Đ$ = 1.12 in pure MeOH, $Đ$ = 1.68 in 30/70 MeOH/H_2O), indicating a clear loss of control in aqueous environments. Uncontrolled polymerization was also reported for Cu(0) wire mediated RDRP of HEA in water, in which it was noted that an insoluble gel formed around the wire at the beginning of the reaction.[45]

In contrast, Cu wire catalyzed polymerization of PEGA in water has been reported to proceed to high conversions (>90%) with good control ($Đ$ ~ 1.25).[46] Utilization of halide salts has also enabled controlled polymerization of PEGA at ppm copper concentrations.[47] 2-(hydroxypropyl) methacrylamide, a monomer of considerable interest due to the biocompatibility and non-toxic nature of its polymers, has been reported to proceed in water in a copper wire catalyzed polymerization, however dispersities were around 1.4.[48]

5.2 In-situ Generation of Cu(0) by Disproportionation of Cu(I)

In 2013 Haddleton and coworkers introduced a new protocol for Cu(0) mediated RDRP in aqueous media, utilizing *in-situ* generation Cu(0), where Cu(0) is formed from the rapid disproportionation of Cu(I) *prior* to addition of monomer and initiator.[9a] The disproportionation equilibrium of Cu(I) in water in the presence of aliphatic tertiary amine ligands is extremely high, with k_{disp} of the order of 10^6. This is altered when an excess of complexing ligand is present, dependent on the relative stabilization of Cu(I)X/L species to Cu(II)X_2/L species. By utilizing Me_6Tren, a ligand which greatly stabilizes Cu(II) in water, Cu(I)Br was shown to disproportionate in pure water on a timeframe of a few seconds (figure 7), generating metallic Cu(0) particles and Cu(II)Br_2/Me_6Tren. This disproportionated mixture was subsequently deoxygenated by 'sparging' with nitrogen for up to15 minutes. An aqueous deoxygenated solution of monomer and alkyl halide initiator was then injected into the predisproportionated catalyst mixture triggering polymerization. Control over polymerizations was shown to be excellent, with dispersities below 1.10 even at quantitative monomer conversion.

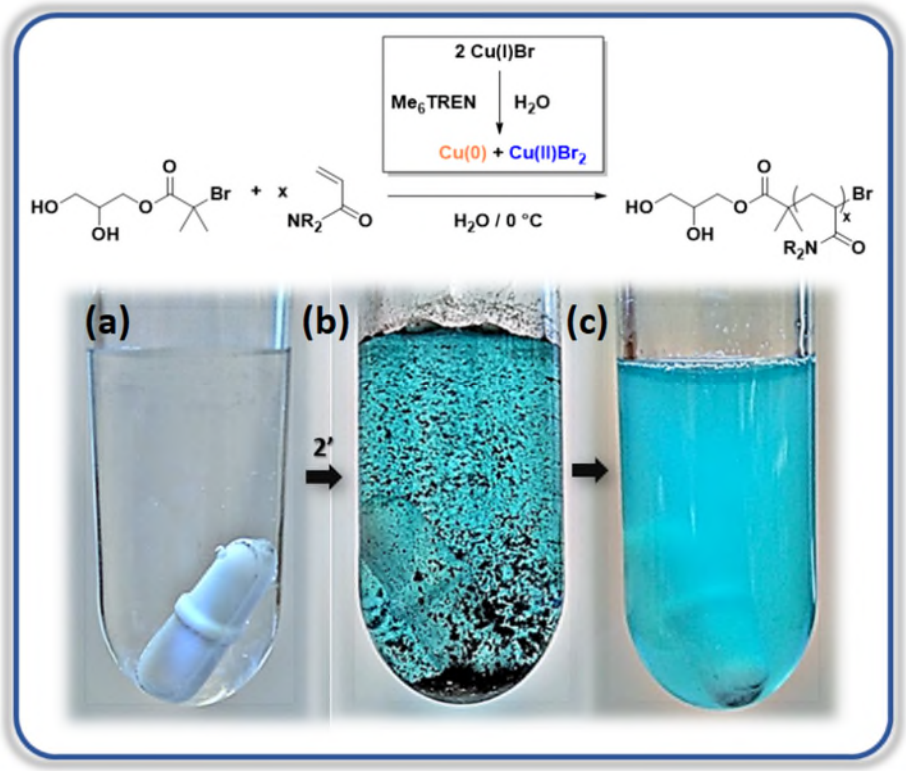


Figure 7: Polymerization of an acrylamide *via* pre-disproportionation of Cu(I)Br. (a) aqueous solution of Me_6Tren. (b) Cu(0) particles and Cu(II) complex after addition of Cu(I)Br. (c) solution after addition of monomer and initiator. Figure in part adapted with permission from reference 49c. Copyright 2016 Royal Society of Chemistry.

Numerous monomers have been successfully polymerized using this technique, including various acrylamides,[9a, 49] acrylates, methacrylates,[50] methacrylic zwitterionic monomers,[51] polyoxazoline macromonomers,[52] and glycomonomers[53] at room temperature or below. A significant advantage of the pre-disproportionation protocol is the ability to control the synthesis of poly(acrylamides), a class of monomer shown to be problematic for many by traditional ATRP techniques in both aqueous and organic media. The reaction has been demonstrated to be tolerant to multiple functional groups, with examples of controlled polymerization in biologically relevant aqueous environments such as PBS and blood serum.[54] In addition to this the Haddleton group also reported controlled Cu(0)-RDRP in alcoholic beverages (mixed ethanol-water binary solvents between 3 and 50 vol% ethanol),[55] in which it was noted that carbonated solvents (including carbonated drinking water) allowed for both controlled polymerization and *in-situ* depolymerization, a very unusual phenomenon which has since been studied in further detail.[56]

Retention of chain-end functionality at conversions close to 100% is not a common feature of Cu mediated RDRP techniques in aqueous media, due to hydrolysis of the alkyl halide ω chain end (see section 2.2). In order to reduce the rate of hydrolysis and increase the end group functionality the polymerizations were performed in an ice bath rather than room temperature. This allowed the synthesis of one-pot block copolymers using a wide range of monomers.[9a, 49] The ability of the technique to provide access to high-order block copolymer architectures was best exemplified by Alsubaie *et al.* yielding decablock copolymers prepared in one pot in very short time periods (Figure 8).[57] Timing of sequential additions of monomer was found to be crucial to controlling polymerization, as leaving the reaction under conditions where [M]~0 leaves the bromide chain end susceptible to hydrolysis and side reactions.[58] Synthesis of other complex macromolecular architectures have also been reported, including multiblock star copolymers by Becer and coworkers[59] and well-defined polymer-protein bioconjugates by Wilson, Davis and Haddleton.[60]

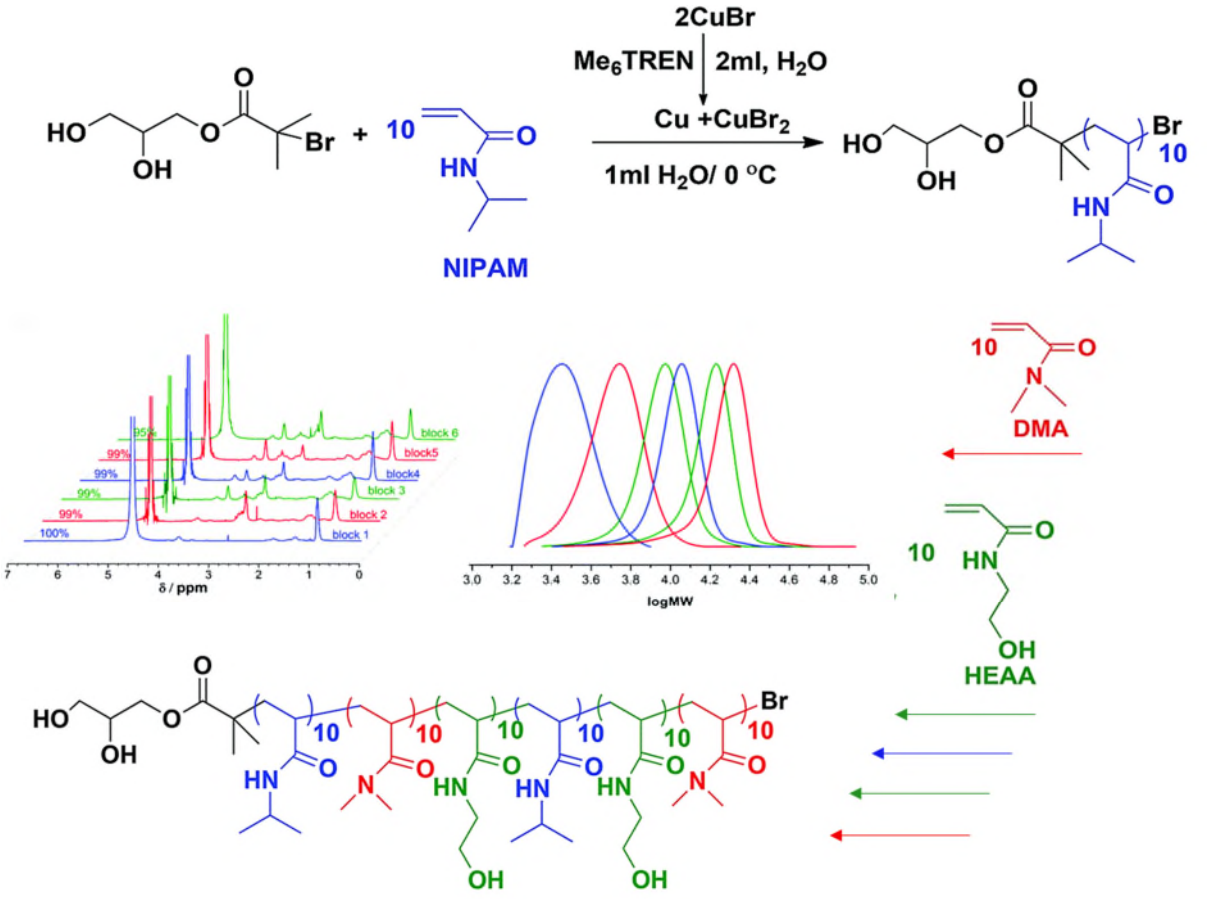


Figure 8. Synthesis of multi-block copolymers composed of NiPAm, DMA and HEAm by iterative Cu(0)-RDRP in H_2O, showing ^1H NMR spectra and evolution of molecular weight by DMF SEC. Figure Adapted with permission from reference 57. Copyright 2015 Royal Society of Chemistry.

Aqueous Cu(0)-RDRP by pre-disproportionation has the distinct benefit of being applicable to a wide range of monomers (particularly acrylamides) and being ideal for *in-situ* block copolymerizations despite the susceptibility of the bromide ω chain end to hydrolysis.[15, 22a] In terms of copper concentration, aqueous Cu(0)-RDRP typically use around 0.4 equivalents of Cu(I)Br relative to initiator, this is an improvement over traditional ATRP techniques which are usually stoichiometric with respect to copper. However it is still significantly higher than activator regeneration ATRP methods which are typically conducted at ppm copper concentrations (~0.02 eq. relative to initiator.)

5.3 In-situ Generation of Cu(0) by Reduction of Cu(II)

In 2016 Monteiro and coworkers reported a novel method of aqueous Cu(0)-RDRP of NiPAm utilizing *in-situ* generated Cu(0) particles obtained *via* reduction of Cu(II)Br_2 with $NaBH_4$.[61] The reduction of Cu(II) to Cu(0) was shown to be quantitative and as a result of this the ratio between Cu(0) and Cu(II) in polymerizations could be tuned by simply changing the stoichiometry between $NaBH_4$ and Cu(II). Polymerization of NiPAm was demonstrated to proceed to conversion close to 100% in just a few minutes with good agreement between theoretical and experimental molecular weights. Furthermore, the end group fidelity was also shown to be high (~95% at conversions approaching 100%) through matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-ToF MS) of samples 'end-capped' by a thio-bromo substitution reaction to eliminate hydrolysis.[14] This technique is one of the few Cu-mediated protocols shown to be effective for polymerizing an acrylamide monomer, however the scope currently only encompasses PNiPAm at relatively low molecular weights (M_n < 5 kDa) with no demonstration of chain extension, despite the high end group fidelity reported.

6. Monomer Scope of Aqueous Cu Mediated RDRP

6.1. Acrylates, methacrylates and acrylamides

The main focus of this review has examined in detail the polymerization of methacrylate, acrylate and acrylamide monomers in aqueous solution; all of which can yield water soluble materials with wide ranging uses. Controlled polymerization of (meth)acrylates has been successful with many of the techniques described, whereas acrylamide polymerization is more problematic, with far fewer reports. However, the development of Cu(0)-RDRP *via in-situ* disproportionation has overcome this limitation, giving controlled polymerization with almost

quantitative conversion and end group fidelity; also yielding similar results for the polymerization of (meth)acrylates.

Successful aqueous Cu-mediated RDRP also enables the polymerization of charged and acidic monomers, which often have poor solubility in organic solvents. The following sections will discuss and examine some of the Cu-mediated RDRP techniques which have enabled advances in the polymerization of challenging monomers, for example monomers containing cationic amine moieties, acidic groups, and zwitterionic characteristics.

6.2 Charged Monomers

Due to the limited solubility of charged and zwitterionic monomers in organic solvents, the polymerization of this monomer family is typically limited to aqueous solution, with many examples carried out in solvent mixtures commonly of water with DMF, MeOH or isopropanol. The polymerization of these monomers and aqueous media in general is incompatible with anionic polymerization and is also challenging with controlled radical polymerization conditions vary significantly between those used for positive, negative and zwitterionically charged monomers. These monomers can often be hygroscopic, difficult to handle, and contain acidic functionalities (see subsequent section), for example sulfonates and phosphonates which can provide further challenges and compete with the ligand for complexation to the copper catalyst.

The first example of the polymerization of a charged monomer in purely aqueous solution was in 2000 by Armes,[62] who reported the polymerization of methacryloxyethyl phosphocholine (MPC). The issues surrounding the spontaneous uncontrolled polymerization of this monomer were overcome by the rapid rate of ATRP polymerization, yielding 90% conversion in 5 minutes at ambient temperature. These reactions utilized a Cu(I)Br, bpy catalytic system and in all cases illustrated a conversion greater than 96%, but only low molecular weights were targeted (less than 10 kDa) and some degree of control was lost at the higher end of this range with dispersity of 1.4 for those greater than 7 kDa. The work was later expanded to higher molecular weights, by fine tuning the ratio of initiator to copper to ligand, yielding higher molecular weights *(M_n* = 22 kDa , dispersity 1.26).[63] The group subsequently showed the presence of end group fidelity by chain extension of PMPC (DP_{20}, 99% conversion, M_n = 6 kDa, Đ = 1.12) with OEGMA generating a well-defined block copolymer (M_n = 16 kDa, *Đ* = 1.27),[64] and also illustrated the first example of a block copolymer of two zwitterionic polymers, by incorporating [2-(methacryloyloxy)ethyl]dimethyl(3-sulfopropyl)ammonium

hydroxide (SBMA) as the second block. Note however that higher molecular weights, and a broader scope of block copolymers could only be achieved by utilizing methanol or methanol water mixtures.[63, 65] The copolymerization of SBMA (also known as *N*,*N*-dimethyl-*N*-methacryloyloxyethyl-N-sulfobutyl ammonium (DMBS)) and acrylamide has also been reported utilizing Cu(0)-RDRP in aqueous media, utilising Cu(0) powder and $CuCl_2$/Me_6Tren as the catalyst.[66] Both PMPC and PSBMA were homopolymerized by Simula *et al*,[51] utilizing the predisproportionation of Cu(I)Cl in the presence of Cu(II)Cl and PMDETA.

Other reports of charged methacrylates include the synthesis of well-defined poly(2-[(methacryloyloxy)ethyl]trimethylammoniumdimethylaminoethyl methacrylate chloride)(MeDMA) (the quaternized form of PDMAEMA) in aqueous solution utilizing aqueous ATRP, with a Cu(I)Br catalyst and bpy as the ligand at room temperature.[67] All reactions proceeded to high conversions (>90%) and were reasonably well controlled with dispersities of 1.20-1.30. However, similarly to previous reports, to prepare well-defined block copolymers solvent mixtures of water with methanol or isopropanol was required. Later, the synthesis of star polymers of MeDMA were reported with similar polymerization conditions.[68]

The most successful report to date is the polymerization of acryloyl phosphatidyl chloride (APC), a zwitterionic acrylate monomer containing ammonium and phosphate functionalities *via* aqueous Cu(0)-mediated LRP, generating PAPC up to DP_{50} with dispersities in the range of 1.07-1.22.[49b] This is the only example of a zwitterionic polymer synthesized with Cu-mediated RDRP that has a dispersity of less than 1.10, but as in previous cases increasing the molecular weight further resulted in a reduction in conversion and a loss of control. However, charged or zwitterionic acrylamides and methacrylamides are even less explored than methacrylates and acrylates, with the only example up to date being the use of carboxybetaine functionalized acrylamide and methacrylamides by Edlund et al, utilizing Cu(0) wire, a hemicellulose macroinitiator and Me_6Tren as the ligand.[69] Pseudo first order kinetics were observed for both monomers, with conversions of greater than 90% achieved suggesting a good degree of control over the process, however no SEC data was reported. Further examples are limited to solvent mixtures, with poly(3-acrylamidopropyl)-trimethylammonium chloride synthesised and chain extended in water ethanol mixtures *via* Cu(0)-RDRP, illustrated high end group fidelity at 90% conversion yielding block copolymers with a dispersity of around 1.30.[70]

There are many remaining challenges in the synthesis of charged polymers in pure water *via* Cu-mediated RDRP, with limited successful reports to date. The synthesis of block copolymers and molecular weights higher than 15 kDa for homopolymers is challenging with broad dispersities common, showing there are many remaining avenues of improvement to optimize this important group of monomers.

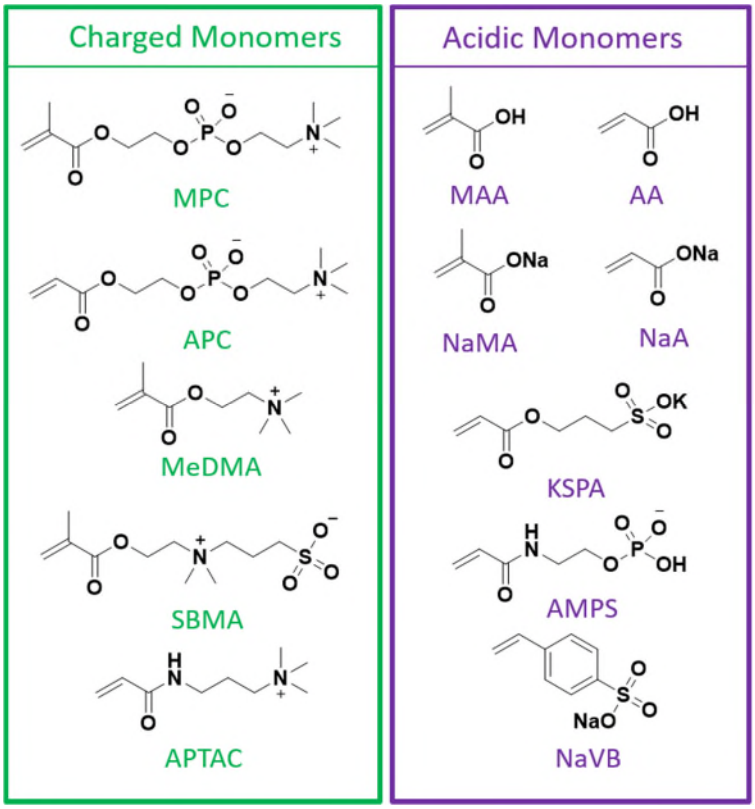


Figure 9. Examples of charged and acidic monomers successfully polymerized by aqueous Cu-mediated RDRP.

6.3 Acidic Monomers

Polymerization of acidic monomers by Cu-RDRP is challenging in both organic and aqueous media. Most reports of controlled polymerizations are of monomer salts, in which the acidic moiety is not protonated (figure 9).

The first example of ATRP of an acidic monomer was by Armes and coworkers in 1999.[19] NaMA, the sodium salt of methacrylic acid (MAA), was polymerized in aqueous media using Cu(I)Br and bpy. Molecular weights of up to 7.3 kDa were successfully prepared with good conversions (50-80%) with a high degree of control ($Đ$ = 1.20-1.30) However, targeting higher molecular weights resulted in a loss of control with $Đ$ > 2. pH was found to be a critical parameter for successful polymerization as no polymerization was observed below pH 6, at which point bpy becomes protonated. This is a dramatic change from free radical

polymerization, in which it is favourable to polymerize MAA at low pH, to avoid a build-up of anionic charge on the polymer backbone. The same group also reported the polymerization of sodium 4-vinylbenzoate in aqueous solution (pH 11), using Cu(I)Br as the catalyst, a PEG functionalized isobutyrate or sodium 4-(bromomethyl)benzoate as an initiator at ambient temperature, illustrating linear kinetics and an M_n close to theory, even at very high conversions (>95%, Đ =1.30).[71]

Cu(0)-RDRP utilizing predisproportionation of Cu(I)Br has been reported to be efficient for the polymerization of the sodium salt of 2-acrylamido-2-methylpropane sulfonic acid (NaAMPS), an important monomer in a variety of biological and industrial applications.[72] Nikolaou *et al.* demonstrated the polymerization of NaAMPS with molecular weights up to 30 kDa with dispersities below 1.30.[49b] A monomer with similar functionality, sulfopropyl acrylate potassium salt (KSPA), was reported to polymerize with a similar degree of control utilizing the predisproportionation of Cu(I)Br in the presence of Me_6Tren with a dispersity of 1.20 for DP_{40}. As target DP was increased beyond 80, control was also lost with dispersities greater than 1.50 illustrated in all cases. Low molecular weight PKSPA has also been successfully reported by photoinduced ATRP.[6b]

Direct polymerization of acidic monomers in their protonated form, such as MAA or acrylic acid (AA), was commonly considered to be impossible for most copper mediated RDRP systems, due to protonation of the ligand at the low pH required. Even in organic media only a small amount of MAA can be copolymerized whilst retaining control.[73] Direct polymerization is attractive as k_p can be higher for the protonated monomer (10 times higher in the case of MAA *vs.* NaMA),[74] polymerization is not inhibited by build-up of anionic charge on the polymer backbone, complexation to copper will be significantly lessened, and no titration of the final product is required. In 2015 Fantin *et al.* conducted an electrochemical investigation into three commonly used catalyst systems in aqueous ATRP: CuX/Me_6Tren, CuX/PMDETA, and CuX/TPMA, and found that polymerizations of PEGMA with TPMA could proceed effectively at low pH (1.5).[75] This apparent stability at low pH was subsequently used to demonstrate the polymerization of MAA in acidic aqueous solution using *e*ATRP and Cu(0)-RDRP (figure 10).[76] Conducted at low pH (~1), poly(MAA) was prepared with molecular weights up to 87 kDa, with varying degrees of control ($Đ$ = 1.33->2.0). However, initiator efficiencies varied significantly, in some cases being greater than 100%. Despite the high conversions attained in some cases, no chain extensions are reported either *in-situ* or from an isolated PMAA macroinitiator.

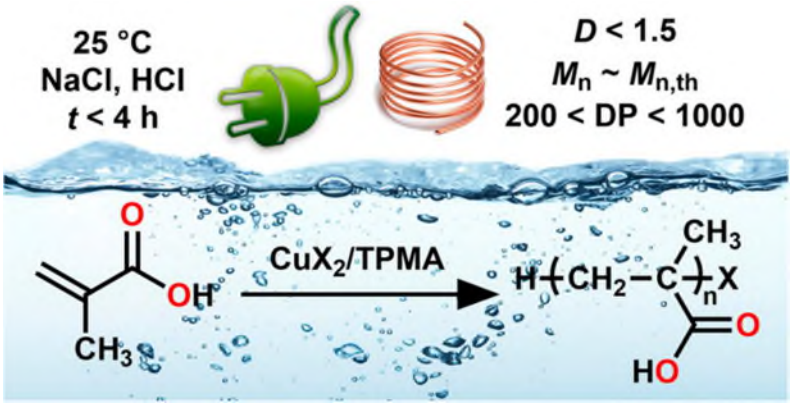


Figure 10. Aqueous e-ATRP and Cu(0)-RDRP of MAA. Figure reprinted with permission from reference 76. Copyright 2016 American Chemical Society.

6.4 Current Limitations of Aqueous Cu-mediated RDRP

Despite the massive advancements made in controlled polymerization in aqueous media using copper catalysts, there are still a number of challenges to be overcome, most of which relate to monomer scope; some classes of monomer have yet to be polymerized with high degrees of control.

Polymerization of *N*-vinyl monomers such as *N*-vinyl pyrrolidone (NVP) is challenging by Cu-mediated RDRP; this is due to lack of resonance stabilization of the generated radicals and strongly electron donating pendant groups, which makes them highly reactive and means that end group fidelity is compromised by radical-radical termination, chain transfer reactions and hydrolysis.[77] Few reports also exist of the successful polymerization of methacrylamides, either in aqueous or organic media, with results in aqueous media showing linear kinetics but a lack of control over molecular weight distributions ($Đ$ = 1.47->2.0).[48] These two monomer classes could be particularly useful as their polymers exhibit good water solubility and can exhibit interesting biological behaviour.[48, 78] The controlled polymerization of charged monomers to high molecular weights with degrees of control similar to uncharged water soluble monomers is another key area that needs development in the field of aqueous Cu-mediated RDRP.

7. Summary and Outlook

Aqueous Cu-RDRP has seen very encouraging advances since the first report of ATRP in aqueous media. Many techniques have been developed which yield high levels of control over chain length, molecular weight distribution, and macromolecular architecture. Activator regeneration methods in ATRP allow catalyst concentrations on a ppm level to be utilized to

give better control than ever before, and the advent of aqueous Cu(0)-RDRP has made great advancements in the synthesis of block copolymers thanks to retention of halide end groups at quantitative monomer conversions. However, a number of challenges still remain. Important classes of monomers such as NVP and methacrylamide that yield biologically relevant polymers are still relatively poorly reported in Cu-RDRP and have not been optimized to the same extent that other monomer classes have, with work to date reporting mostly uncontrolled polymerizations. There are also limited successful reports of the polymerization of acidic and charged monomers in solution and no examples of block copolymer synthesis with protonated acidic monomers. Further challenges surrounding the uncontrolled spontaneous polymerization of zwitterionic monomers in water has also not been surmounted. Techniques which have demonstrated excellent qualities such as ultra-low catalyst loadings and high conversions have often only been optimized for one or two monomer classes. An ideal aqueous transition metal mediated system able to control the polymerization of a wide range of (meth)acrylates, (meth)acrylamides, charged, acidic and *N*-vinyl monomers to quantitative conversions with high end group fidelity at ppm catalyst concentrations still remains elusive.

Author Information

Glen Jones graduated from the University of Warwick (MChem, July 2014) with a final year project on the synthesis and end group modification of star polymers. He is currently a final year PhD student in the Haddleton group at the University of Warwick working on the development of controlled polymerization techniques in aqueous media. His current research interests include: Cu(0) mediated polymerization, photochemistry, and water soluble polymers.

Athina Anastasaki is currently a Global Marie Curie and an Elings Fellow working alongside Professor Craig Hawker at the University of California, Santa Barbara. Prior to this appointment, she completed her PhD studies in the University of Warwick under the supervision of Professor Dave Haddleton and she was awarded (by RSC) the prize for the best PhD in Polymer Chemistry in the UK (2015). Her research focuses on controlled radical polymerization strategies for the synthesis of complex architectures for a wide range of applications.

Richard Whitfield was born in the town of Grantham, Lincolnshire and commenced his chemistry studies at Durham University, receiving his Master's degree in 2014. He completed a final year project under the supervision of Dr. Ezat Khosravi utilizing thiol-ene click chemistry in the synthesis of thermosetting materials for coating applications. Later that year Richard joined the group of Professor David Haddleton to undertake a PhD at the University of Warwick, developing copper mediated polymerization strategies. His further research interests include polymer/RNA complexation and release strategies.

Nikolaos Engelis graduated from the Chemistry Department of the National and Kapodistrian University of Athens in 2013. The following year he graduated from the taught MSc of Polymer Chemistry at the University of Warwick. During that time he worked on Cu(0)-RDRP. Subsequently he started a PhD under the supervision of Professor David Haddleton. His current research focuses on controlled radical polymerization, mainly in emulsion.

Evelina Liarou was born in Athens, Greece, in 1991. She graduated from the University of Patras in 2014. In 2016, she received her Master's Degree (1st Class Honours) in Polymer Chemistry from the University of Athens, where she worked on multifunctional polypeptides and drug delivery systems, under the supervision of Professor Hermis Iatrou. As of October 2016, she is a PhD student at the University of Warwick under the supervision of Professor David Haddleton, focusing on polymer-protein conjugates, drug delivery systems and controlled radical polymerization.

David Haddleton was born in Birmingham, UK in 1962. He graduated from the University of York in 1986 with a PhD in organometallic photochemistry under the supervision of Professor Robin Perutz FRS. He spent time in industry at ICI and has been at the University of Warwick since 1993 promoted to full Professor in 1998. He leads a thriving and challenging team of young scientists at Warwick University, is currently CSO of a spin off company Medherant Ltd concerned with transdermal drug delivery. He was Editor in Chief of the RSC journal Polymer Chemistry until 2017.

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